Comments of A. Judson Wells, PhD., Kennett Square, PA

Executive Summary

Comment 1:

Table ES.2 on page ES-11 should include incident cases of breast cancer. The number of cases for breast cancer can be estimated by using the combined odds ratios from the two best breast cancer studies (Morabia, et al., 1996, and Johnson , et al., 2000). Their combined OR is 1.67 (95% CI, 1.29-2.16). Alternatively, one could combine the ORs from the four best studies by adding Smith, et al., 1994 and Kropp, et al., 2002. This results in an OR of 1.68 (95% CI, 1.36-2.08). However, the latter result is more heavily weighted toward younger women.

Response:

Comment noted. We are concerned that it may be quite difficult to estimate attributable risk given the number of known risk factors for breast cancer that contribute to the high rate of this disease including age at menarche, age at menopause, age at first birth, parity, and whether the woman breast fed her babies. Although perhaps a relatively crude attributable risk could be developed, we felt it was best to avoid the calculation until we have a better way to account for these other known risk factors.

Comment 2:

I find the range for excess lung cancer deaths from ETS in Table ES.2, 411-1,514 for California and 7,564-26,473 for the U. S. to be higher than I thought to be reasonable. On page 7.76 in the report the range is said to be 283 to 1052 deaths for California. Assuming the population of California is about 10% of the U. S. population, this would translate to about 2,830-15,200 for the U. S. The 1992 U. S. EPA report estimated lung cancer deaths from ETS exposure for the whole country at 3,000 for never smokers plus former smokers.

Response:

We have reviewed and updated the attributable risk calculations for lung cancer utilizing the method of U.S. EPA from the 1992 report. This now replaces the previous calculation and is presented in detail in the revised document.

Comment 3:

I also wondered if there is any way to include all causes of death from exposure to ETS, either here or in Part B. There are all cause data in Gillis et al, Eur J Respir Dis 1984;65 (suppl 133):121-126 on males, 1.04 (95% CI, 0.69-1.57), and females, 1.33 (95% CI, 0.94-1.89), in western Scotland. In the extensive data that Hirayama sent me in 1988 (referred to in the breast cancer section in B) there are also all cause data for women in Japan. The age adjusted RR is 1.17 (95% CI, 1.11-1.24). There may be other sources of all cause data. I just haven't looked. It also might be an occasion to honor G. S. Miller who is the pioneer in investigating deaths from passive smoking. In the Journal of Breathing, 1978;41:5-8, he reported that nonsmoking wives in Erie County, Pennsylvania, who were married to nonsmokers lived 4 years longer (78.8 versus 74.7) than wives married to smokers. This was 2+ years before the 1981 reports of Hirayama and Trichopoulos on ETS and lung cancer.

Response:

The current update of the OEHHA document (OEHHA, 1997) did not in general include additional consideration of studies that were published during the time period reviewed previously (prior to 1996). Additionally, we have decided not to include a category of "all causes of death" as it is felt to be too broad a definition to be helpful in our current review of the scientific literature.

Part A

Comment 4:

Pages III-4 and 5. There has been too little attention paid in the U. S. to the work of Pritchard et al, Environ Technol Lett 1988;9:545-552, at Harwell in England on what happens to aged, diluted ETS. They labeled tobacco smoke with a radioactive isotope of iodine in 1-iodohexadecane, which boils at 380 degrees C., about in the middle of the boiling point of tobacco tar. They used a 14.4 m3 chamber and found that, during aging

and dilution, 70% of the particulate ETS tar evaporates into the vapor phase. Vapor phase tar, like other organic vapors (Bond et al, Toxicol Appl Pharmacol 1985;78:259-267) would deposit quantitatively in the lung, and the lung has no clearance mechanism for vapor phase deposits, whereas only about 15% of the particulates deposit in the lung, the remainder being exhaled. This phenomenon could go a long way toward explaining why the passive risk is so similar to the active risk in non-contact sites like the heart and breast. It appears that the tar compounds that would evaporate would have molecular weights in the 100 to 200 range which would include quinoline, ethyl quinoline, benzoquinoline, phenanthridene, nornicotine, beta-naphthyl amine, nitroso pyrolidine, nitroso nornicotine, pyrene, fluoranthene, phenol, the cresols, 2,4-dimethyl phenol, catechol, and the methyl catechols, all of which have some carcinogenic activity.

Response:

ARB staff have responded to this comment in their summary of the comments on Part A.

Part B

Comment 5:

On page 4-6 in the discussion of McMartin et al., 2002 there is no mention of the significance of higher nicotine in the SIDS babies, but not higher cotinine. This means that the relevant exposure occurred during a very short time before the death occurred, namely, during the half-life of nicotine.

Response:

Thank you for pointing out this important fact. The review has been edited to mention this.

Comment 6:

In Chapter 6 there is no mention of Chronic Obstructive Lung Disease (COLD) as an outcome of ETS exposure. I know of two such reports. Kalandidi et al. Lancet, 1987;Dec 5:1325-26, found that never smoking wives married to smokers had incidence ORs of 1.3 (95% CI, 0.7-2.3) with exposure to less than 300,000 husband's cigarettes in their lifetime, and 1.7 (95% CI, 0.8-3.4) for exposure to more than 300,000 cigarettes, versus wives married to nonsmokers. Hirayama, in the 1988 personal communication referred to above, found an age adjusted RR of 1.32 (95% CI, 0.8-2.1) for death from emphysema or bronchitis when his Japanese wives were married to a smoker vs. a nonsmoker. There may be other references, but I haven't looked.

Response:

The purpose of the current document is to examine more recently published findings, which may extend or modify conclusions reached in the 1997 document. Unless it has been considered essential to our findings we have not included reviews of work prior to 1997.

Comments on Chapter 7 (Cancer):

(General & all cancers)

Comment 7:

In Chapter 7, Table 7.0B there is no mention of radioactive polonium which I remember as a component of ETS, and which I believe is carcinogenic.

Response:

OEHHA thanks the commenter for pointing out this omission. IARC Monographs Vol 78 (2001) identified all internally deposited α-emitting radionuclides as carcinogenic to humans (Group I), and also found sufficient evidence of carcinogenicity in animals specifically for polonium-210 (lung cancer in hamsters). 210Po is responsible for over 99% of the α-activity in tobacco smoke (IARC, 2001, citing Cohen et al., 1980). Table 7.0B will be amended by the following addition to reflect these data:

^{210}Polonium (0.04-0.1 μCi) (7)	Sufficient	Sufficient	Vol. 78, pp. 465-477. (Group 1 listing is of all internally deposited α-emitting radionuclides, considered as a group).

7. US EPA (1992)

Comment 8:

On page 7-10 the reference to the EPA report as Wells (1992) could be more specific by listing it as (Wells, 1992b) and referencing it as Wells AJ (1992b), In: U.S. EPA (1992)

Respiratory Health .....Washington, DC., Appendix B. Reference1992a should be reserved for my 1992 letter in Am J Epidemiol, which goes with the 1991 letter in AJE.

Response:

The citation has been clarified in the text and table of references as suggested.

Comment 9:

You will probably be criticized if you don't refer to the work of tobacco consultant Peter Lee, who still doesn't agree that misclassification of smokers as nonsmokers is a small effect.

Response:

OEHHA has separately received a number of comments from Mr. Lee, and will be responding to these both directly and, where appropriate, by additions to the document text.

Comment 10:

On page 7-12 the 1997 report missed the all cancer passive smoking data in Gillis et al., Eur J Respir Dis 1984;65 (suppl 133):121-126. They report on 44 male cancer deaths and 144 female cancer deaths. In my 1988 paper in Environment International, Wells AJ (1988), Environ Int 1988;14:249-265, the risks from cancers other than lung (five studies) and lung cancer are reported separately, but they are easily combined to get total cancer results. My paper in J Women's Cancer 2000;2(2):55-66, Table 1, also gives a total cancer risk of 1.4 (95% CI, 1.1-1.8) by combining the results from various studies.

Response:

The current update of the OEHHA document (OEHHA, 1997) did not in general include additional consideration of studies that were published during the time period reviewed previously (prior to 1996). In addition, we feel that while the findings are interesting, that there is little added to our review by combining data in a meta-analysis over such a broad category of outcomes as total cancer risk.

Comments on Lung cancer:

Comment 11:

On page 7-67 mention should be made about the errors in underlying studies of lung cancer from workplace ETS exposure, specifically Wells AJ et al., J Natl Cancer Inst 1997;89:821-822 on errors in Garfinkel et al (1985), and Wells (1998b) on errors in Janerich, et al., (1990).

Response:

Both the specific studies criticized were described in the 1997 document: it is not clear that they deserve further individual consideration in this update. The current document refers to the more general considerations by citing OEHHA (1997) and Wells (1998b). This reference has been expanded by including the sentence:

"Some of the earlier non-positive meta-analyses were affected by exposure estimation inconsistencies and errors in reporting of the underlying studies, or inappropriate weighting factors applied in the meta-analyses, as described in detail by Wells and Henley (1997) and Wells (1998b)."

Comment 12:

On page 7-74 the meta-analysis in Wells 1998b of 15 studies, RR = 1.19 (95% CI, 1.07-1.34), should be added to the list in the first paragraph even though it covers only workplace exposure.

Response:

The citation has been added, with the list re-ordered by date.

Comments on Breast cancer:

Comment 13:

On page 7-93 the statement that Millikan's ORs for current smoking are versus never active/passive of 1.0 (0.7-1.4) and following is wrong. Those ORs in their Table 2 are

versus all never smokers, except for the ETS result at the bottom of the table. At the top of page 7-94 the "limitations" should include not using non-ETS exposed never smokers in the referent for the main OR's as well as the age 18+ referent for the passive smoking OR.

Response:

The passage has been modified as follows:

No association was observed between breast cancer and current active smoking versus never smokers in all women [adjusted OR 1.0 (95% CI 0.7-1.4)] in premenopausal women [adjusted OR 0.9 (95% CI 0.5-1.5)], or in postmenopausal women [adjusted OR 1.2 (95% CI 0.7-2.0)] (see Table 7.4A). The authors note that "when we excluded women with exposure to ETS from the referent group, ORs for active smoking were unchanged or slightly attenuated."

Comment 14:

On page 7-97, Marcus et al., I would add "all" to the last word in line 6. Also it should be noted that the ETS results in their Table 2 are for smokers as well as nonsmokers.

Response:

All has been inserted as suggested. The data presented in this section is from their table 3.

Comment 15:

On page 7-101 there is a reference to Wells, 2002 (should be 2003), but this reference does not appear in the reference list on page 7-203. The reference is Wells AJ. Breast cancer and tobacco smoke [letter]. Br J Cancer 2003;89:955.

Response:

The correction has been made in the document.

Comment 16:

On page 7-102, last line, add "all" to never-smokers. The 1.60 RR on the next page is probably crude. The adjusted RR in Table II is 1.61 (95% CI, 1.19-2.19). It would also be worth including their RR for exposure for 40+ years and 20+ cigarettes per day of 1.83 (95% CI, 1.29-2.61).

Response:

The correction has been made in the document.

Comment 17:

On page 7-104, another weakness of the Band et al., study is that they did not consider using non-ETS exposed never-smokers as their referent.

Response:

The section has been changed as follows:

Limitations of the study include lack of consideration of time-since-first-exposure in the dose-response analysis of pack-years and lack of data concerning ETS and thus including ETS exposed in the referent population (potentially biasing results towards the null).

Comment 18:

On page 7-103 under Terry, et al., 2002a, mention should be made of their observation that 40+ cigarettes per day yields a RR of 1.34 (95% CI, 1.06-1.69) and that 40+ years and 20+ cigarettes per day yields 1.83 (95% CI, 1.29-2.61). Also Terry, et al., should be included in Table 7.4B. Mention in the active smoking section might be made of Couch, et al., Cancer Epidemiol Biomark Prev 2001;10:327-332, that women with a family history of three or more cases of breast or ovarian cancer had a breast cancer RR of 2.4 (95% CI, 1.2-5.1) for ever smokers relative to never smokers. Also Manjer, et al., Int J Cancer 2001;91:580-584, report that women with estrogen receptor-negative breast tumors have RRs of 2.21 (95% CI, 1.23-3.96) for current smokers and 2.67 (95% CI, 1.41-5.06) for former smokers, relative to women who have never smoked. I believe there is other evidence that women with estrogen-negative tumors are at higher risk from tobacco smoke.

Response:

Thank you for pointing out the additional papers, which have been added to the review.

The table has been modified to include data from Terry.

Comment 19:

In Table 7.4B there is no referent shown for Lash and Aschengrau (1999), Kropp and Chang-Claude (2002), or Lash and Aschengrau (2002). In Table 7.4C on page 7-118 there is no referent shown for Morabia et al. (2000). These should all be "No active/passive". Also I have a letter from Sarah Smith in which she says, referring to their paper, Smith et al., (1994), that ever smokers not exposed to other's ETS had an OR of 2.00 (95% CI, 0.98-4.12) compared with non-ETS exposed never smokers. This information was published in Wells (1998b).

Response:

Referents for Lash and Aschengrau (1999), Kropp and Chang-Claude (2002), Lash and Aschengrau (2002), and Morabia et al. (2000) have been added.

Comment 20:

In pages 7-119 and following the reference Wells (1998) should be changed to Wells (1998b).

Response:

The reference to Wells (1998) appears now to be correct as a result of corrections applied to the table of references (compare the responses to Comments 8 and 9).

Comment 21:

On pages 7-120 and 7-121 re the Smith et al., (1994) paper the risks shown were taken from their Table IV, which is for smokers and nonsmokers exposed to ETS. Even though there is less statistical significance in individual categories because of the smaller numbers, I think CalEPA ought to go with the numbers in Smith's Table V for the effects of ETS exposure on never smokers only. Throughout the literature the passive smoking risk that is sought is that for ETS-exposed never smokers relative to non-ETS exposed never smokers. One could set up separate studies of the effect of ETS exposure on smokers, but the two should never be combined. The high statistical significance that

you show for lifetime exposure based on Table V in Smith, et al., 2.53 (95% CI, 1.19-5.36) is good enough. The whole paragraph should be rewritten.

Response:

This paragraph has been modified.

Comment 22:

On page 7-122 there is a reference to Terry et al., 2002. There are two Terry 2002 references in the reference list, page 7-202. Here you probably mean 2002b since there are no passive smoking data in 2002a. Also on page 7-122 there is no mention of Zhao et al., Matched case control study for detecting risk factors of breast cancer in women living in Chengdu (in Chinese). Chung Hua Liu Hsing Ping Hsueh Tsa Chih (Clin J Epidemiol, probably for China) 1999;20:91-94, nor of Lui et al., Passive smoking and other factors at different periods of life and breast cancer risk in Chinese women who have never smoked - a case control study in Chongqing, People's Republic of China. Asian Pacific J Cancer Prev 2000;1:131-137, both of which contain data on passive smoking and breast cancer as indicated in Table 7.4E, but there are no explanatory paragraphs for them in pages 7-123 to 7-131, nor are they included in the reference list, pp 7-198, 7-204.

Response:

The Terry et al. citation has been changed. Zhao and Liu have been added.

Comment 23: The best thing to do with Marcus et al, (2000) pages 7-126 and 127, is to omit it from the passive smoking part of the report. There are no good passive smoking data in it. All of the exposed groups include smokers as well as never smokers. See discussion above under Smith et al. In the OR where the referent is "no exposure and no history of active smoking" the smokers were eliminated in the referent, but, based on the cell counts, the smokers are still included in the exposed group.

Response:

The following qualifier has been appended to the description of the Marcus study.

"However, these data are of limited usefulness in evaluation of passive smoking risk to non-smokers since, though the unexposed category is limited to never smokers, the exposed category includes both never and ever active smokers."

Comment 24:

Under Morabia, et al., (2000 and 1998) on page 7-127, would it be helpful to refer to Figure 7.4.3 toward the end of the first paragraph. Under Wartenberg, et al., (2000) at the top of page 7-129, the wording could be a little more definite. Try "Nevertheless, since the ETS exposures other than from spouse were included in the questionnaire only at one point in time, namely, at enrollment, the potential for...." Under Nishino, et al., (2001) page 7-129, mention should be made of their statement on page 801 of their paper that "women were not asked about their marital status in the baseline survey, so most unmarried women, who are a high-risk group for breast cancer, were categorized as not being passive smokers. This may have been why the breast cancer risk was lower with passive smoking exposure".

Response:

The wording has been modified as indicated in the comment.

Comment 25:

On page 7-132, under Khuder and Simon, there is an error in the paper. From their Table 2 the actual ORs for the lowest levels of exposure range from 0.80 (Wartenberg) to 3.10 (Morabia), and for highest levels, from 1.10 (Warternberg) to 3.20 (Morabia). K & S is a very sloppy paper. For example they include Marcus, et al., in the dose response list with only one value. Also the RR for Wartenberg in Table 1 is wrong.

Response:

The risk values cited have been corrected.

Comment 26:

On page 7-135, Table 7.4D, a footnote on what the IARC classifications mean would be helpful.

Response:

This information has been added to the text and to the footnotes.

Comment 27:

Also why are Delfino, et al., Egan, et al., and Wartenberg, et al., excluded from Figure 7.4.2?

Response:

The figure 7.4.2 is meant to present studies that have gathered exposure information for various sites and time periods (lifetime exposure). The above studies do not meet those criteria.

Comment 28:

On page 7-137, Nishino, et al., is also a new prospective study. Jee, et al., has dose response, 1.2, 1.3, and 1.7. Both Lui, et al., 2000 and Zhao, et al., 1999 are listed on page 7-137, but the are no descriptions of these studies in the earlier text, nor are they listed in the reference list on pages 7-198 and 7-204. Why is Millikan, et al., missing from Table 7.4E? Why is Kropp, et al., labeled "likely" in Table 7.4E and "unlikely" in Table 7.4F? Also Hirayama and Jee are "unlikely " in Table 7.4E and "likely" in Table 7.4F. On page 7-140 it is stated that there are 15 studies. Actually there are 16 studies; Millikan is missing from Table 7.4E and Lui from Table 7.4F, Figure 7.4.4 and Table 7.4G.

Response:

The indicated wording changes have been made and descriptions of the studies by Zhao and Liu added. Liu has not been added to Table 7.4F because of our concerns about some of the data that were felt to be possibly inconsistent and our inability to get those concerns clarified by the author.

Comment 29:

In Table 7.4I, page 7-149, under Delfino, et al., isn't it better to use their low risk controls (60 cases) yielding a passive OR of 1.78 (95% CI, 0.77-4.11). In Table 7.4J there is no referent shown for Lash, et al., 1999, 40/139, or for Lash, et al., 2002, 80/53.

Response:

Thank you for pointing this out, the table has been adjusted to use Delfino's low risk number which is more appropriate. Referents have been added to Table 7.4J.

Comment 30:

I find Tables 7-4I and 7.4J confusing. If Table 7.4I is supposed to include all of the case-control studies, it is missing Morabia, Smith, Liu, Sandler, Zhao, and Lash 2002. As noted above, I would omit Marcus. If Table 7.4J is supposed to include the case-control studies with dose-response, it is missing Morabia, Smith (child only, adult only, child plus adult) and Liu. On page 7-154, Table 7.4L, Hirayama and Nishino are missing. Also the word "Deaths" in the heading for Cases should be removed in both Tables 7.4L and 7.4M because some of the cohort studies used diagnosis. In Jee, the RR for wives exposed to current smokers for more than 30 years (1.7, 95% CI, 1.0-2.8) should be added to both Tables 7.4L and 7.4M.

Response:

The indicated additions and changes have been made.

Comment 31:

In the reference list on page 7-203, Wells AJ 1991, 1992a, 1998a, and 2001 should be designated as letters. Also there is an Erratum associated with 1998a, which is noted at Am J Epidemiol 1998;148(3):314.

Response:

The reference list has been modified as indicated.

Comment 32:

As a general comment on ETS and breast cancer, I know that your general plan is to discuss active smoking first, then passive smoking, and finally biological plausibility. This makes sense for lung cancer, but for breast cancer the reverse may be better. Start with the exposure windows, probable hormonal effects, and animal studies of breast specific carcinogens. Then get into passive smoking, and finally into active smoking. The advantage of this order is that it explains why the active smoking effect depends so much on the referent that is used, either including or excluding passively exposed never smokers, and it leads to an explanation of why the passive effect is almost as large as the active effect.

Response:

The revised version of the report does give greater attention to the relationship between active and passive smoking. The organization of chapters was kept as close as possible to

that seen in the 1997 document so that the reader can refer to the corresponding section of that document easily.

Comments on Chapter 8

Comment 33:

In Chapter 8, Table 8.1, page 8-3, and in the text on pages 8-10 and following, the comments on Wells (1998) are restricted to workplace exposure only. Actually there is an Appendix in that paper which updates Wells' 1994 meta-analysis (J Am Coll Cardiol 1994;24:546-554). The update includes 19 studies that were available at that time, and breaks the results down by morbidity and mortality, males, females and both genders, four quality tiers, and exposure from spouse only, home only, and all adult exposures. The quality tiers were taken from my 1994 meta-analysis (above) and were based on the number and importance of the other risk factors that were adjusted for. The combined RR for morbidity for tier 1, the top quality tier, and all adult exposures for males plus females is 1.86 (95% CI, 1.20-2.88). For all home exposures only, the combined RR is 1.63 (95% CI, 1.22-2.18), and for spouse exposure only, it is 1.39 (95% CI, 1.06-1.82). This demonstrates that better questionnaires lead to higher RRs, and that the real relative risk may be nearer 1.8 than 1.25. For mortality, tier 1, males and females combined, the RR for all adult exposures is 1.87 (95% CI, 0.56-6.20), but for many fewer cases. For spouse exposure only for mortality for all studies combined, the RR is 1.21 (95% CI, 1.09-1.35), in reasonable agreement with the other meta-analyses, but less than the 1.8 from the better studies.

Response:

The table and text in chapter 8 have been modified to include the results in the appendix of that paper.

Comment 34:

On page 8-6, Table 8.1 under Raitakari, et al., it looks like ETS in the third column needs to be lowered one line. On pages 8-16/17 I could find no reference in the description of You, et al., to Figure 8.03. On pages 8-32/33/35 on platelet effects and animal studies there is no mention of the rather thorough discussions on these subjects in the 1997 report. Even with a mention of those discussions, you may want to refer to some of that work. I am thinking particularly about the work of Burghuber, et al., and Davis, et al., on platelets, Zhu, et al., on rabbits, and Penn, et al., on cockerels.

Response:

Raitakari was fixed in Table 8.1. There is a reference to Fig 8.03 in You on page 8-20. Regarding reference to works in the previous document, the following sentence appears on pg 8-36: The effect was also observed in studies by Sinzinger and Kefalides (1982) and Burghuber et al. (1986). These studies, described in Cal/EPA (1997), document a significant decrease in platelet sensitivity to the anti-aggregatory effects of PGI2 among nonsmokers but not active smokers following acute smoke exposure. Since this volume is meant as a supplement and update to the 1997 document, we have not reviewed material previous examined other than where it was felt essential for the readers understanding.

Comment 35

All in all it is a very good report.

Response:

Thank you for your comments.